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(54) Title: USE OF ION CHANNEL MODULATING AGENTS FOR TREATING PAIN

(57) Abstract: The present invention relates to the use of a particular group of compounds, formerly known for their potassium channel modulating properties, as pain-relieving agents.

USE OF ION CHANNEL MODULATING AGENTS FOR TREATING PAIN

TECHNICAL FIELD

The present invention relates to the use of a particular group of compounds, formerly known for their potassium channel modulating properties, as pain-relieving agents.

BACKGROUND ART

Recent studies focusing on pain transduction mechanisms have shown that ion channels, in particular Na^+, VR1, ASIC, and $P2X_3$-channels, play a key role in the pathology of chronic pain. Normally sensory information acts at specialised ion channel complexes located upon C- or Aβ-sensory neuron endings to elicit noxious (pain-inducing) and non-noxious (non pain inducing) transmission to the CNS. In the setting of tissue injury, these same stimuli result in increased sensory transmission to the CNS due to the sensitising actions of peptides, cytokines and prostaglandins on ion channel function.

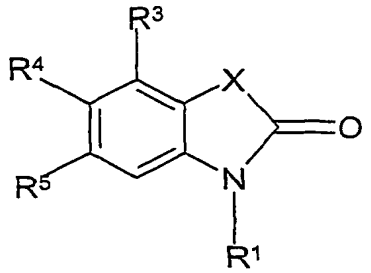
Thus C-fibres transmit increased noxious information (hyperalgesia), and Aβ-fibres can also encode noxious information (allodynia).

WO 00/34248 describes chemical compounds capable of modulating potassium channels, and their use for the treatment or alleviation of diseases or conditions responsive to modulation of SK_{Ca}, IK_{Ca} and/or BK channels, including diseases or conditions like respiratory diseases, certain CNS-related diseases and for reducing or inhibiting undesired immunoregulatory actions. Apart from migraine, which is supposed relieved through their action on smooth muscles, these potassium channel modulators are not reported to have any potential for relieving pain.

SUMMARY OF THE INVENTION

According to the present invention it has now been found that a particular group of chemical compounds, formerly known as potassium channels modulators, are found useful for combating pain.

In its first aspect the invention relates to the use of chemical compounds of Formula I



(I)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

X represents NR^2, O or S; wherein R^2 represents hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$; or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V, independently of one another, represent hydrogen and/or alkyl; or a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^1 represents hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$; or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V, independently of one another, represent hydrogen and/or alkyl; or a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; and/or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; or

R^5 is as defined above and R^3 and R^4 together form an additional 4 to 7 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl;

for the manufacture of a pharmaceutical composition for the treatment or alleviation of pain.

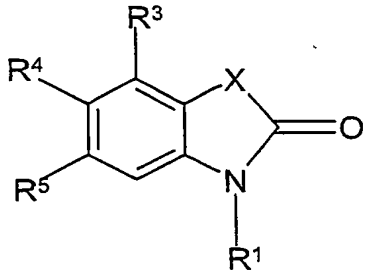
In further aspects, the invention provides pharmaceutical compositions comprising the compounds for use according to the invention and methods for the treatment or alleviation of pain.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

According to the present invention it has now been found that a particular group of chemical compounds, formerly known as potassium channels modulators, are useful for combating pain.

The pain-relieving compounds for use according to the invention may be characterised by Formula I,



(I)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

X represents NR^2, O or S; wherein

R^2 represents hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$; or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V, independently of one another, represent hydrogen and/or alkyl; or a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^1 represents hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$; or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V, independently of one another, represent hydrogen and/or alkyl; or a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; and/or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; or

R^5 is as defined above and R^3 and R^4 together form an additional 4 to 7 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may

optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

In a preferred embodiment X represents NR^2, O or S.

In another preferred embodiment R^1 represents hydrogen, alkyl, cycloalkyl, hydroxy, alkoxy, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V independently represents hydrogen or alkyl; or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and R^2 represents hydrogen, alkyl, cycloalkyl, a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy.

In a third preferred embodiment R^1 and R^2, independently of one another, represent hydrogen and/or alkyl.

In a fourth preferred embodiment R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V, independently of one another, represent hydrogen and/or alkyl; or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and R^2 represents hydrogen, alkyl, cycloalkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy.

In a fifth preferred embodiment R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and R^2 represents hydrogen, alkyl, cycloalkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a phenyl or benzyl group.

In a sixth preferred embodiment R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; and/or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from

halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; or R^5 is as defined above and R^3 and R^4 together form an additional 4 to 7 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

In a seventh preferred embodiment R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, phenyl and/or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; or R^5 is as defined above and R^3 and R^4 together form an additional 5 to 6 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

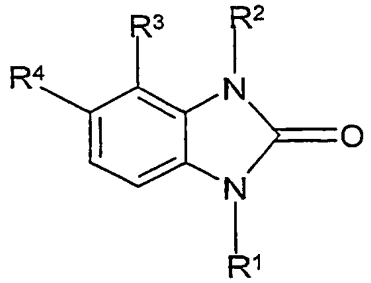
In an eight preferred embodiment R^5 represents hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3 or carboxy; and R^3 and R^4 together form an additional 5 to 6 membered, fused ring selected from cyclohexan, benzen, thiadiazol, piperidin and pyridin.

In a ninth preferred embodiment R^3 represents hydrogen, hydroxy, alkoxy, halo, NO_2 or CF_3; R^4 represents hydrogen, alkoxy, halo, NO_2, CN or CF_3; and R^5 represents hydrogen, alkyl, NO_2, halo or carboxy.

In a tenth preferred embodiment R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, halo, nitro, cyano and/or trifluoromethyl.

In an eleventh preferred embodiment R^3 and R^4, independently of one another, represent hydrogen, halo, nitro, cyano and/or trifluoromethyl; and R^5 represents hydrogen.

In a twelfth preferred embodiment the compound for use according to the invention is a benzimidazolone derivative represented by Formula II



(II)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^2 represents hydrogen, alkyl, cycloalkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a phenyl or benzyl group; and R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, phenyl and/or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

In a thirteenth preferred embodiment the compound for use according to the invention is a compound of Formula II wherein R^1 represents a C_{1-6}-alkyl group; R^2 represents hydrogen, a C_{1-6}-alkyl group or a cycloalkyl group; and R^3 and R^4, independently of one another, represent halo, nitro, cyano and/or trifluoromethyl.

In a most preferred embodiment the compound for use according to the invention is

1-Ethyl-4,5-dichlorobenzimidazol-2-one; or

1,3-Diethyl-4,5-dichloro-benzimidazol-2-one;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

In a fourteenth preferred embodiment the compound for use according to the invention is a compound of Formula I wherein

X represents O or S;

R^1 represents hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy;

R^2 represents hydrogen, alkyl, cycloalkyl, phenyl, benzyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; and

R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, phenyl and/or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; or

R^5 is as defined above and R^3 and R^4 together form an additional 5 to 6 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it

may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

In a fifteenth preferred embodiment the compound for use according to the invention is a compound of Formula I wherein

R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl or benzyl;

R^2 represents hydrogen, alkyl or cycloalkyl; and

R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy and/or phenyl.

In a most preferred embodiment the compound for use according to the invention is

3-Ethyl-5-chlorobenzoxazolone;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

In a sixteenth preferred embodiment the compound for use according to the invention is a compound of Formula I wherein R^3 and R^4 together form a fused pyridine ring, which pyridine ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN and CF_3.

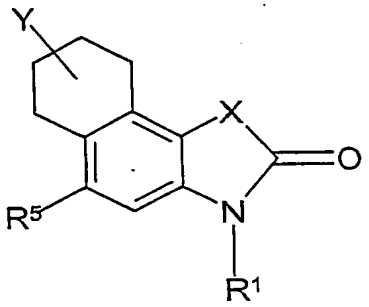
In a seventeenth preferred embodiment the compound for use according to the invention is a compound of Formula I wherein R^1 and R^2, independently of one another, represent hydrogen and/or alkyl; and R^5 represents hydrogen.

In a most preferred embodiment the compound for use according to the invention is

3-Ethyl-quinolino[5,6-d]imidazolinone;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

In a nineteenth preferred embodiment the compound for use according to the invention is a compound of Formula III



(III)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

X, R^1 and R^5 are as defined in claim 1; and

Y represents hydrogen, halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

In a twentieth preferred embodiment the compound for use according to the invention is a compound of Formula III wherein X represents NR^2 or O; R^1 and R^2, independently of one another, represent hydrogen and/or alkyl; and R^5 represents hydrogen.

In a most preferred embodiment the compound for use according to the invention is

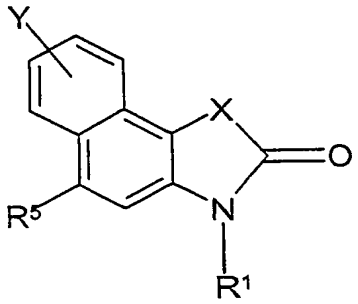
5,6,7,8-Tetrahydronaphto[1,2-d]imidazolinone;

1,3-Diethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone; or

1-Ethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

In a twenty-first preferred embodiment the compound for use according to the invention is a compound of Formula IV



(IV)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

X, R^1 and R^5 are as defined above; and

Y represents hydrogen, halo, NO_2, CN, CF_3 or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

In a twenty-second preferred embodiment the compound for use according to the invention is a compound of Formula IV, wherein X represents NR^2 or O; R^1 and R^2, independently of one another, represent hydrogen and/or alkyl; and R^5 represents hydrogen.

In a most preferred embodiment the compound for use according to the invention is

3-Ethyl-naphto[1,2-d]oxazolinone;

3-Ethyl-naphto[1,2-d]imidazolinone; or

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

In a twenty-third preferred embodiment the compound for use according to the invention is a compound of Formula I, wherein R^3 and R^4 together form a 5

membered heterocyclic fused ring, which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN and CF_3.

In a twenty-fourth preferred embodiment the heterocyclic ring is a 1,2 or 4-imidazolyl, 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazol-3,4 or 5-yl, thiazol-2,4 or 5-yl, or 2 or 3-thienyl.

In a twenty-fourth preferred embodiment R^1 and R^2, independently of one another, represent hydrogen, alkyl and/or benzyl; and R^5 represents hydrogen.

In a most preferred embodiment the compound for use according to the invention is

3-Benzyl-(2,1,3-thiadiazolo)[4,5-g]benzimidazolone;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

Definition of Substituents

In the context of this invention halo represents a fluorine, a chlorine, a bromine or a iodine atom.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to twelve carbon atoms (C_{1-12}-alkyl), more preferred of from one to six carbon atoms (C_{1-6}-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In a most preferred embodiment alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms (C_{3-7}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention a hydroxy-alkoxy group designates an alkoxy group as defined above, which alkoxy group is substituted with one or more hydroxy groups. Preferred hydroxy-alkoxy groups of the invention include 2-hydroxy-ethoxy, 3-hydroxy-propoxy, 4-hydroxy-butoxy, 5-hydroxy-pentoxy and 6-hydroxy-hexoxy.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above.

In the context of this invention an alkoxy-alkyl group designates an "alkyl-O-alkyl-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkyl groups of the invention include methoxy-methyl, methoxy-ethyl, ethoxy-methyl, and ethoxy-ethyl.

In the context of this invention a carbocyclic ring is a group holding carbon only as ring atom. The ring structure may in particular be aromatic (i.e. a benzene ring), or a saturated 5-6 membered cycloalkane ring.

In the context of this invention a heterocyclic group is a cyclic group, which holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). The ring may in particular be aromatic (i.e. a heteroaryl), saturated or partially saturated. Preferred heterocyclic monocyclic groups of the invention include 5- and 6 membered heterocyclic monocyclic groups.

Examples of preferred aromatic heterocyclic monocyclic groups of the invention include 1,3,2,4- or 1,3,4,5-dioxadiazolyl, dioxatriazinyl, dioxazinyl, 1,2,3-, 1,2,4-, 1,3,2- or 1,3,4-dioxazolyl, 1,3,2,4- or 1,3,4,5-dithiadiazolyl, dithiatriazinyl, dithiazinyl, 1,2,3-dithiazolyl, 2- or 3-furanyl, furazanyl, 1,2 or 4-imidazolyl, isoindazolyl, isothiazol-3,4 or 5-yl, isoxazol-3,4 or 5-yl, 1,2,3-, 1,2,4-, 1,2,5- or 1,3,4-oxadiazol-3,4 or 5-yl, oxatetrazinyl, oxatriazinyl, 1,2,3,4- or 1,2,3,5-oxatriazolyl, oxazol-2,4 or 5-yl, 2 or 3-pyrazinyl, 1,3 or 4-pyrazolyl, 3 or 4-pyridazinyl, 2,3 or 4-pyridinyl, 2,4 or 5-pyrimidinyl, 1,2 or 3-pyrrolyl (azolyl), 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazol-3,4 or 5-yl, thiazol-2,4 or 5-yl, 2 or 3-thienyl, 1,2,3-, 1,2,4- or 1,3,5-triazinyl, and 1,2,3-, 1,2,4-, 2,1,3- or 4,1,2-triazolyl. Most preferred heterocyclic groups are 1,2 or 4-imidazolyl, 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazol-3,4 or 5-yl, thiazol-2,4 or 5-yl, and 2 or 3-thienyl.

Examples of preferred saturated or partially saturated heterocyclic monocyclic groups of the invention include 1,3,5,6,2-dioxadiazinyl, 1,2,3,4,5-, 1,2,3,5,4-dioxadiazolyl, dioxanyl, 1,3-dioxolyl, 1,3,5,6,2-dithiadiazinyl, 1,2,3,4,5- or 1,2,3,5,4-dithiadiazolyl, 2-isoimidazolyl, isopyrrolyl, isotetrazolyl, 1,2,3- or 1,2,4-isotriazolyl, morpholinyl, oxadiazinyl, 1,2,4-, 1,2,6-, 1,3,2-, 1,3,6- or 1,4,2-oxazinyl, piperazinyl, homopiperazinyl, piperidinyl, 1,2-, 1,3- or 1,4-pyranyl, and 1,2,3-pyrrolidinyl.

Pharmaceutically Acceptable Salts

The pain-relieving compounds of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzensulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the formate derived from formic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the sulphate derived from sulphuric acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a pain-relieving compound for use according to the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of pain-relieving compounds for use according to the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

The pain-relieving compounds for use according to the invention may be provided in unsolved or solvated forms together with pharmaceutically acceptable solvents such as water, ethanol, and the like. Solvated forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, solvated forms are considered equivalent to unsolved forms for the purposes of this invention.

Steric Isomers

The pain-relieving compounds for use according to the invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The pain-relieving compound for use according to the invention may also be resolved by the formation of diastereomeric amides by reaction of the pain-relieving compound with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the pain-relieving compound for use according to the invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Biological Activity

According to the present invention it has now been found that a particular group of chemical compounds, formerly known as potassium channels modulators, are found useful for combating pain.

These compounds are also found to be capable of reducing the action of C-fibres, which mechanism may be – without limiting the scope of the invention – the mechanism by which they act as pain-relieving agents.

The pain-relieving activity of the compounds for use according to the invention may be determined by standard methods, e.g. *Stein et al.*, Pharmacol. Biochem. Behav. 1988 **31** 445-451; *Bennett GJ et al.*, Pain 1988 **33** 87-107; *Kingery et al.*, Pain 1989 **38** 321-322; *Seltzer et al.*, Pain 1990 **43** 205-218; *Wheeler-Aceto et al.*, Psychopharmacology 1991 **104** 35; *Chung et al.*, Pain 1992 **50** 355-363; *Chaplan SR et al.*, J. Neurosci. Methods 1994 **53** 55-63; and *Mosconi T et al.*, Pain 1996 **64** 37-57.

The realisation of pain is a multi-dimensional process involving physical, emotional and perceptual integration, the primary function of which is to serve to protect the organism from a potentially tissue-damaging stimulus.

The pain treated or alleviated according to the invention may in particular be

Nociceptive pain, which is the normal (reflex) physiological response to pain. This type of pain occurs with any form of acute pain such as a sharp needle prick against the skin;

Inflammatory pain, which is usually triggered by nociceptive afferents that become irritated when surrounded by inflamed tissue. In most cases, pain sensitivity is proportional to the degree of inflammation and pain generally decreases when the injury heals although the arthritic disorders (osteoarthritis, rheumatoid arthritis) are often an exception to this point. Inflammatory pain also includes fibromyalgia, back pain, cancer pain, irritable bowel pain, post-operative pain, pain associated with viral infection or diseases, with a recognised peripheral or central inflammatory component;

Neuropathic pain, which usually occurs specifically from nerve injury, and which may persist even after the injured nerve has healed, outliving its biological usefulness and compromising the quality of life for the individual. Neuropathic pain is usually associated with e.g. pain arising from any disease state causing damage to the peripheral or central nervous systems, back pain, cancer pain, chemotherapy induced neuropathy, postherpetic neuralgia, fibromyalgia, trigeminal neuralgia, diabetic neuropathy, multiple sclerosis and AIDS pain;

Neurogenic pain, which usually involves dysfunction within the PNS or CNS, and which usually occurs without inflammation, nociception or any particular trauma; and

Tension-type headache.

Moreover the pain may be acute or chronic pain. In this respect chronic pain is a ubiquitous term generally defined as pain that persists beyond the usual course of an acute disease, or beyond a reasonable time for an injury to heal that recurs at intervals of months or years.

Finally, in the context of this invention migraine is not considered a condition for treatment or alleviation according to the invention, because migraine is believed to be relieved through an action on the smooth muscles.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a pain-relieving compounds for use according to the invention.

While a pain-relieving compound for use according to the invention may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the SK/IK/BK channel modulating agents of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more

pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, and intravenous injection) administration, or those in a form suitable for administration by inhalation or insufflation.

The pain-relieving compound, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The pain-relieving compound for use according to the invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing the pharmaceutical compositions of the invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate,

magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The pain-relieving compound for use according to the invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include

solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the pain-relieving compound may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions which exhibit large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

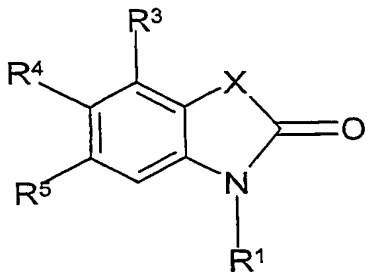
In another aspect the invention provides a method for the treatment or alleviation of pain in living animals, including humans, which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a pain-relieving compound as described above.

The pain for treatment or alleviation according to the invention may in particular be nociceptive pain, inflammatory pain, neuropathic pain, neurogenic pain, acute pain or chronic pain.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

CLAIMS

1. Use of a chemical compound of Formula I



(I)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

X represents NR^2, O or S; wherein

R^2 represents

hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$; or

a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V, independently of one another, represent hydrogen and/or alkyl; or

a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^1 represents

hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$; or

a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V, independently of one another, represent hydrogen and/or alkyl; or

a phenyl or a benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^3, R^4 and R^5, independently of one another, represent

hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; and/or

a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; or

R^5 is as defined above and R^3 and R^4 together form an additional 4 to 7 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl;

for the manufacture of a pharmaceutical composition for the treatment or alleviation of pain.

2. The use according to claim 1, wherein

X represents NR^2, O or S.

3. The use according to either one of claims 1-2, wherein

R^1 represents

hydrogen, alkyl, cycloalkyl, hydroxy, alkoxy, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V independently represents hydrogen or alkyl; or

a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^2 represents hydrogen, alkyl, cycloalkyl, a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy.

4. The use according to either one of claims 1-2, wherein R^1 and R^2, independently of one another, represent hydrogen and/or alkyl.

5. The use according to either one of claims 1-2, wherein

R^1 represents

alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, carboxy, $-CH_2CN$, $-CH_2C(=NOH)NH_2$, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a group of the formula $-CH_2CONR^{IV}R^V$, wherein R^{IV} and R^V, independently of one another, represent hydrogen and/or alkyl; or

a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^2 represents

hydrogen, alkyl, cycloalkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy.

6. The use according to claim 5, wherein

R^1 represents

alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^2 represents

hydrogen, alkyl, cycloalkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a phenyl or benzyl group.

7. The use according to any one of claims 1-6, wherein

R^3, R^4 and R^5, independently of one another, represent

hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; and/or

a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; or

R^5 is as defined above and R^3 and R^4 together form an additional 4 to 7 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it

may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula -$SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

8. The use according to claim 7, wherein

R^3, R^4 and R^5, independently of one another, represent

hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, phenyl and/or a group of the formula -$SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; or

R^5 is as defined above and R^3 and R^4 together form an additional 5 to 6 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula -$SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

9. The use according to claim 8, wherein

R^5 represents

hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3 or carboxy; and

R^3 and R^4 together form an additional 5 to 6 membered, fused ring selected from cyclohexan, benzen, thiadiazol, piperidin and pyridin.

10. The use according to any one of claims 1-6, wherein

R^3 represents hydrogen, hydroxy, alkoxy, halo, NO_2 or CF_3;

R^4 represents hydrogen, alkoxy, halo, NO_2, CN or CF_3; and

R^5 represents hydrogen, alkyl, NO_2, halo or carboxy.

11. The use according to any one of claims 1-6, wherein

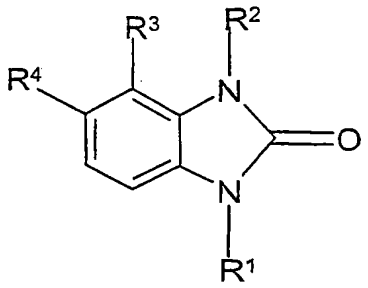
R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, halo, nitro, cyano and/or trifluoromethyl.

12. The use according to any one of claims 1-6, wherein

R^3 and R^4, independently of one another, represent hydrogen, halo, nitro, cyano and/or trifluoromethyl; and

R^5 represents hydrogen.

13. The use according to claim 1, wherein the benzimidazolone derivative is represented by Formula II



(II)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof,

wherein,

R^1 represents

alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy; and

R^2 represents

hydrogen, alkyl, cycloalkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a phenyl or benzyl group; and

R^3, R^4 and R^5, independently of one another, represent

hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, phenyl and/or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

14. The use according to claim 13, wherein

R^1 represents a C_{1-6}-alkyl group;

R^2 represents hydrogen, a C_{1-6}-alkyl group or a cycloalkyl group; and

R^3 and R^4, independently of one another, represent halo, nitro, cyano and/or trifluoromethyl.

15. The use according to claim 14, wherein the compound is

1-Ethyl-4,5-dichlorobenzimidazol-2-one; or

1,3-Diethyl-4,5-dichloro-benzimidazol-2-one;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

16. The use according to claim 1, wherein

X represents O or S;

R^1 represents

hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, hydroxy, hydroxy-alkyl, alkoxy, alkoxy-alkyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; or

a phenyl or benzyl group, which phenyl and benzyl groups may be substituted one or more times with substituents selected from halo, NO_2, CN, CF_3, alkyl, cycloalkyl, hydroxy and alkoxy;

R^2 represents

hydrogen, alkyl, cycloalkyl, phenyl, benzyl, or a group of the formula $-CH_2CO_2R'$, wherein R' represents hydrogen or alkyl; and

R^3, R^4 and R^5, independently of one another, represent

hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy, phenyl and/or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl; or

R^5 is as defined above and R^3 and R^4 together form an additional 5 to 6 membered fused ring, which fused ring may be a carbocyclic or a heterocyclic ring, it may be an aromatic, saturated or partially saturated ring, and which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

17. The use according to claim 16, wherein

R^1 represents alkyl, cycloalkyl, cycloalkyl-alkyl or benzyl;

R^2 represents hydrogen, alkyl or cycloalkyl; and

R^3, R^4 and R^5, independently of one another, represent hydrogen, alkyl, hydroxy, alkoxy, halo, NO_2, CN, CF_3, carboxy and/or phenyl.

18. The use according to claim 17, wherein the compound is

3-Ethyl-5-chlorobenzoxazolone;

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

19. The use according to claim 16, wherein R^3 and R^4 together form a fused pyridine ring, which pyridine ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN and CF_3.

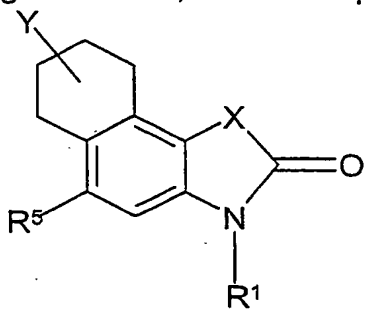
20. The use according to claim 19, wherein

R^1 and R^2, independently of one another, represent hydrogen and/or alkyl; and

R^5 represents hydrogen.

21. The use according to claim 20, wherein the chemical compound is 3-Ethyl-quinolino[5,6-d]imidazolinone;
or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

22. The use according to claim 1, which is represented by Formula III



(III)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

X, R^1 and R^5 are as defined in claim 1; and

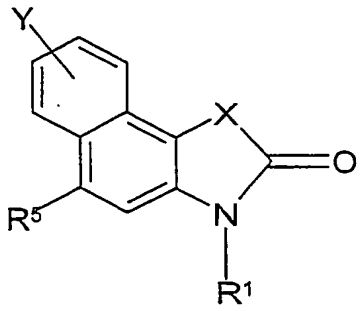
Y represents hydrogen, halo, NO_2, CN, CF_3, or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

23. The use according to claim 22, wherein
X represents NR^2 or O;
R^1 and R^2, independently of one another, represent hydrogen and/or alkyl; and

R^5 represents hydrogen.

24. The use according to claim 23, wherein the compound is
5,6,7,8-Tetrahydronaphto[1,2-d]imidazolinone;
1,3-Diethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone; or
1-Ethyl-5,6,7,8-tetrahydronaphto[1,2-d]imidazolinone;
or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

25. The use according to claim 1, wherein the compound is represented by Formula IV



(IV)

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof, wherein,

X, R^1 and R^5 are as defined above; and

Y represents hydrogen, halo, NO_2, CN, CF_3 or a group of the formula $-SO_2NR''R'''$, wherein R'' and R''', independently of one another, represent hydrogen and/or alkyl.

26. The use according to claim 25, wherein

X represents NR^2 or O;

R^1 and R^2, independently of one another, represent hydrogen and/or alkyl; and

R^5 represents hydrogen.

27. The use according to claim 26, wherein the compound is

3-Ethyl-naphto[1,2-d]oxazolinone;

3-Ethyl-naphto[1,2-d]imidazolinone; or

or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

28. The use according to claim 1, wherein

R^3 and R^4 together form a 5 membered heterocyclic fused ring, which fused ring may optionally be substituted one or more times with substituents selected from the group consisting of halo, NO_2, CN and CF_3.

29. The use according to claim 28, wherein the heterocyclic ring is a 1,2 or 4-imidazolyl, 1,2,3,4- or 2,1,3,4-tetrazolyl, thiadiazol-3,4 or 5-yl, thiazol-2,4 or 5-yl, or 2 or 3-thienyl.

30. The use according to claim 29, wherein

R^1 and R^2, independently of one another, represent hydrogen, alkyl and/or benzyl; and

R^5 represents hydrogen.

31. The use according to claim 30, wherein the compound is
3-Benzyl-(2,1,3-thiadiazolo)[4,5-g]benzimidazolone;
or a pharmaceutically acceptable salt or an oxide or a hydrate thereof.

32. The use according to any of claims 1-31, wherein said pain is nociceptive pain, inflammatory pain, neuropathic pain, neurogenic pain, acute pain or chronic pain.

33. A pharmaceutical composition comprising a therapeuticallly-effective amount of a compound for use according to claims 1-31, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent, for the treatment or alleviation of pain.

34. The pharmaceutical composition of claim 33, wherein said pain is nociceptive pain, inflammatory pain, neuropathic pain, neurogenic pain, acute pain or chronic pain.

35. A method of treatment or alleviation of pain in a living animal body, including a human, comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound according to any of claims 1-25.

36. The method of claim 35, wherein said pain is nociceptive pain, inflammatory pain, neuropathic pain, neurogenic pain, acute pain or chronic pain.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000019

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4184 A61K31/423 A61K31/428 A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, MEDLINE, SCISEARCH, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/34248 A (TEUBER LENE ;NEUROSEARCH AS (DK); STROEBAEK DORTE (DK); CHRISTOPHE) 15 June 2000 (2000-06-15) page 3, line 17 - page 4, line 23 page 19, line 14 - line 25 page 20; table 1 claims 1,5,11,16,19 claim 22	1-36
X	WO 02/085357 A (EURO CELTIQUE SA ;KYLE DONALD (US); SUN QUN (US); VICTORY SAM (US)) 31 October 2002 (2002-10-31) page 13, line 12 - page 19, line 2 page 83; table 3 claims 63-89	1,2,5-8, 10-13, 32-36
A	page 124, lines 2,3; claim 80	3,4,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2004	-2 07 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000019

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 545 845 A (NEUROSEARCH) 1993 page 2, paragraph 1 page 7; table 1 claims 1,2	1-3,5-8, 10-13, 32-36
A	EP 0 477 819 A (NEUROSEARCH) 1998 column 3, line 41 - line 47 column 5, line 42	1-3,5-8, 10-13, 32-36
X	WO 02/053171 A (ALZHEIMER CHRISTIAN; SWITCH BIOTECH AG (DE); GOPPELT ANDREAS (DE);) 11 July 2002 (2002-07-11) claims 8,14	33,34
A	page 85, paragraph 2	1
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P,A	ESTEVEZ MIGUEL ET AL: "The voltage-gated calcium channel UNC-2 is involved in stress-mediated regulation of tryptophan hydroxylase." JOURNAL OF NEUROCHEMISTRY, vol. 88, no. 1, January 2004 (2004-01), pages 102-113, XP001191143 ISSN: 0022-3042 abstract	1-3,5-8, 10-13, 32-36
A	SNUTCH T P ET AL: "Voltage-dependent calcium channels--beyond dihydropyridine antagonists." CURRENT OPINION IN PHARMACOLOGY. ENGLAND FEB 2001, vol. 1, no. 1, February 2001 (2001-02), pages 11-16, XP001191144 ISSN: 1471-4892 abstract page 14, column 2, paragraph 3 - page 15, column 1, paragraph 1	1-3,5-8, 10-13, 32-36

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 872 246 A (KISSEI PHARMACEUTICAL) 21 October 1998 (1998-10-21) column 2, line 40 - line 53 -----	
A	EP 1 221 443 A (BANYU PHARMA CO LTD) 10 July 2002 (2002-07-10) paragraph [0001] -----	

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2004/000019

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 35,36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000019

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International Application No
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